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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,705	09/11/2003	A. Thomas Look	112706.123US2	6046
24395	7590	05/13/2008	EXAMINER	
WILMERHALE/DC 1875 PENNSYLVANIA AVE., NW WASHINGTON, DC 20004				BERTOGLIO, VALARIE E
ART UNIT		PAPER NUMBER		
1632				
NOTIFICATION DATE			DELIVERY MODE	
05/13/2008			ELECTRONIC	

## Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/659,705	LOOK ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 17 March 2008.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1,3,5-17,19-24,31-36,38,40-52,54-59 and 67-74 is/are pending in the application.  
 4a) Of the above claim(s) 3 and 38 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1,5-17,19-24,31-36,40-52,54-59 and 67-74 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 24 February 2004 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)	5) <input type="checkbox"/> Notice of Informal Patent Application
Paper No(s)/Mail Date _____.	6) <input type="checkbox"/> Other: _____ .

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/17/2008 has been entered.

Claims 2,4,18,25-30,37,39,53 and 60-66 have been cancelled. Claims 3 and 38 are withdrawn as being drawn to nonelected, patentably distinct species. Claims 1,5-8,24,31,35-36,40-43,67-69 are amended. Claims 1,3,5-17,19-24,31-36,38,40-52,54-59 and 67-74 are pending. Claims 1,5-17,19-24,31-36,40-52,54-59 and 67-74 are under consideration in the instant office action.

#### *Specification*

The disclosure is objected to because of the following informalities: The specification contains several references to a URL (for example: page 21, line 4). The attempt to incorporate subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference (See MPEP 608.01(p)). Appropriate correction is required.

#### *Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Enablement*

Claims 1,5-17,19-24,31-36,40-52,54-59 and 67-74 remain rejected under 35 U.S.C. 112, first paragraph. The specification, while being enabling for 1) a transgenic fish whose genome comprises a transgene comprising a cMyc gene operably linked to the Rag2 promoter wherein cMyc is expressed in T-lymphocytes of the fish resulting in cMyc-induced T-cell lymphoblastic leukemia and 2) a method of screening drugs or agents that mediate cMyc-induced T-cell lymphoblastic leukemia comprising contacting said transgenic fish with a test drug or agent and comparing the phenotype of said contacted fish to that of said fish prior to contact with said test drug or agent , wherein a decrease in cMyc-induced lymphoblastic leukemia in the contacted fish compared to that prior to contact with said test drug or agent indicates a potential drug or agent for decreasing cMyc-mediated T-cell lymphoblastic leukemia, does not reasonably provide enablement for 1) a transgenic fish whose genome comprises any oncogene operably linked to any lymphoid-specific promoter wherein any leukemia or lymphoma results or for 2) a method of using said fish as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection is maintained for reasons of record set forth at pages 3-8 of the office action dated 11/22/2006.

The claims, as amended, are broadly drawn to a transgenic fish comprising a transgene encoding any oncogene operably linked to any lymphoid-specific promoter. Dependent claims limit the genera of promoters and oncogenes, for example to T-cell specific promoter. Claims 24 and 35 are drawn specifically to a transgenic fish whose genome comprises a cMYC gene operably linked to a RAG2 promoter. Claims 1,24 and 35 now require that the fish exhibit an induced leukemia or lymphoma, which

remains a broad genus of phenotypes. Claims 36,40-52,54-59 and 67-74 are drawn to screening methods using the claimed fish.

The specification has taught generating transient transfected and germline transgenic zebrafish expressing a mcMYC transgene operably linked to the zebrafish Rag2 promoter, in T-cells. mcMYC, EGFP-mcMYC, and MYC-ER (page 41, paragraph 2), constructs were used in independent experiments. Each cMyc construct led to leukemic phenotypes in the fish, including the MYC-ER construct in the absence of tamoxifen, albeit at a lower frequency. The specification has not taught the genus of transgenic fish encompassed by the claims or methods of using them. Examples 3-5 provide prophetic teachings of developing other transgenic fish models of cancers. However, the specification does not provide the guidance necessary to make any transgenic fish expressing any oncogene other than cMYC under the control of the RAG2 promoter, in detail sufficient enough to overcome the unpredictability that is well-established in the art of making transgenic animals.

The unpredictability in the art is set forth at page 5, last paragraph-page 7 of the office action dated 11/22/2006. In general, the unpredictabilities relevant to the instantly claimed invention are with respect to the phenotype that is caused by expression of a transgene, the activity of promoters and the levels of expression and spatial/temporal expression control the promoter will cause. With this in mind, and given the guidance in the specification, it would not have been predictable at the time of filing what phenotypic effect any of the claimed transgenes would have other than the expression of cMYC under the control of the RAG2 promoter as taught by the specification. Given the lack of predictability of various promoters in transgenic fish, it is also not predictable that any given transgene will be expressed.

Furthermore, the specification clearly establishes that the Rag2-Myc transgenic expressing fish exhibit T-cell acute lymphoblastic leukemia (see page 455, lines 15-16). The specification does not support that the cMYC overexpressing fish exhibited any other type of lymphoma or leukemia as claimed. In fact, post-filing art supports that the leukemic phenotype in the Rag2-cMyc fish was specific to T-cells

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and began as a thymic lymphoma and progressed to T-cell acute lymphoblastic leukemia (Langenau, 2005, *PNAS*, 102:6068-6073, specifically paragraph bridging pages 6069-70 and Figure 1; Langenau, 2003, *Science*, 299:887-890).

Applicant's arguments have been fully considered and are not fully persuasive.

Applicant argues that the claims are amended and are directed to a transgenic fish whose genome comprises an oncogene operably linked to a *lymphoid specific* promoter, wherein the oncogene is expressed in lymphoid cells and induces leukemia or lymphoma.

The claims are narrowed in scope and now require use of a lymphoid specific promoter as opposed to any promoter. Such a genus encompasses any B-cell or T-cell specific promoter. The claims also narrow the scope of the phenotype to an induced leukemia or lymphoma as opposed to any oncogenic phenotype. Some claims now require expression of the oncogene.

Applicant argues that there are at least two working examples of the claimed transgenic fish. In example 1, Applicant argues there is an exemplification of a transgenic expressing the cMYC operably linked to the Rag2 promoter wherein the oncogene (cMYC) induces lymphoblastic leukemia or lymphoma. Example 2 exemplifies use of a Rag2 promoter driven Bcl2 transgene that results in B-cell transformation. The phenotype resulting from overexpression of Bcl2 differs from that of overexpression of Myc. However, the relevance of this example is not clear as Applicant has elected the *patently distinct* species cMYC and Rag2.

Applicant argues that the person of ordinary skill in the art at filing would recognize that fish lymphoid-specific promoters could express a B- or T- cell oncogene in lymphoid cells at levels sufficient to cause leukemia or lymphoma.

In response, Applicant has provided two examples of a promoter/oncogene combination that leads to a phenotype that is associated with cancers. This is not sufficient to demonstrate that any, or even

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a significant number, of oncogenes will cause such phenotypes when operably linked to any, or even a significant number, of heterologous lymphoid-specific promoters. The art has established a significant unpredictability of transgene effect related to conservation of gene function and regulation of heterologous gene promoters, as well as other effects of general nature to transgenesis. The claims are very broad with respect to the identity of the transgene and the phenotypic effect observed. The specification fails to provide enough guidance such that one of skill would know which oncogene and which promoter will result in any given or desired phenotype. Post-filing art has demonstrated the various effects of different transgenes in fish. Each promoter/oncogene combination resulted in a different oncogenic phenotype (rhabdomyosarcoma, melanoma, etc; see Sabaawy, **PNAS**, 2006, 103:15166-15171; Langenau, 2007, **Genes and Development**, 21:1382-1395; Patton, 2005, **Current Biology**, 15:249-254; Yang, 2004, **Cancer Research**, 64:7256-7262). One of skill in the art would not only need to make the fish and determine if a phenotype of lymphoblastic leukemia or lymphoma is caused, but also it must be determined what effect the transgene has on the fish such that one of skill in the art could determine how to use the fish.

Grounds of rejection specific to the method claims (claim 36 and dependent claims; claim 74) were previously set forth at page 8 of the office action dated 11/22/2006. Applicant has amended claim 36 to include a comparison step and to limit the claim to screening for agents that suppress oncogene-induced lymphoma or leukemia. These aspects of the rejection are withdrawn. However, the claim still fails to recite that the transgene be expressed. Recitation of "wherein expression of the oncogene leads to leukemia..." at line 6 would address this aspect of the rejection. Other grounds of rejection set forth above remain applicable.

*Written Description*

The rejection of claims 18 and 53 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is rendered moot by the cancellation of the claims.

*New Matter*

The rejection of claims 1,2,4-24 and 26-35 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of Applicant's amendments to the claims.

The rejection of claims 36-37,39-59 and 67-74 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of Applicant's amendments to the claims.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 18 and 53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is rendered moot by the cancellation of the claims.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio, Ph.D./  
Primary Examiner  
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